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A CONTRIBUTION TO THE PROBLEM OF THE ORIGIN OF NITROSAMINES AFTER INHALATION OF NITROGEN OXIDES

[K otazce vzniku nitrosaminu po vdechovani kyslicniku dusiku]

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A CONTRIBUTION TO THE PROBLEM OF THE ORIGIN OF NITROSAMINES AFTER INHALATION OF NITROGEN OXIDES

The carcinogenic effect of nitroso compounds, and of nitrosamines in particular, is well-known. The possibility that these compounds form as a result of the action of nitrogen oxides on lung tissue has been assumed on the grounds that nitrosamines in tobacco smoke develop as a result of the reaction between NO_2 and amino compounds, and that the amino groups of pulmonary proteins, or their decomposition products, therefore could be also nitrosylated. Serfontein (1966), Neurath (1967) and Tomatis (1967) found traces of nitrosamines in tobacco smoke, but not in lung tissue.

We here have concerned ourselves with the problem of the effect of nitrogen oxides on the organism, and also have looked into the possibility of the origin of nitroso compounds and nitrosamines in the exposed lungs of animals.

MATERIAL AND METHOD.

White female rats were exposed to nitrogen oxides, some for long periods of time at concentrations used in previous experiments [4], some for short periods when concentrations were increased to develop acute poisoning.

Exposed in all were:

(a) 19 rats for 8 weeks to a concentration of 0.01 mg NO_2/1 (5 ppm);

(b) 50 rats for 3 hours at a time to concentrations of 0.0018, 0.033,

0.057, 0.090, 0.120 and 0.500 mg NO_2/1 (9 ppm - 60 ppm, to 250 ppm, when acute poisoning set in).

Equal numbers of control groups were maintained at all times.

After exposure had ended, the animals were bled to death under an ether anesthetic by cutting the carotids. The lungs were removed and homogenized.

Lung homogenates were extracted with water, lye, ether, acetone, benzene, hexane, and, qualitative determinations of nitro and nitroso groups were made by the usual methods of organic analysis [3], by chromatography [6], and by the use of the Sander method, which is based on the knowledge that UV radiation decomposes nitrosamines and forms well-demonstrated nitrites [7], directly in the extracts, or after chromatographic separation. The latter two methods provide for demonstrating 1 mg of nitrosamine.

The applicability of the processes used was monitored by using homogenized lungs with the preaddition of control materials, nitroso methyl urea, nitroso hydroxy proline, nitrophenol, and dinitrophenyl hydrazine, separately, or in mixtures.

The in vitro experiments conducted involved keeping the lung homogenate in an approximately 15% concentration of NO_2 gas for 3 hours. The possibility of nitroso compounds originating directly in lung tissue as a result of the use of greatly increased concentrations of gas was tested in this manner.

RESULTS AND DISCUSSION.

a) Experiments in vitro.

The presence of nitroso compounds and of nitrosamines was demonstrated in extracts made with ether, hexane, and acetone. The presence of nitro groups also was demonstrated in these extracts, as in an aqueous extraction.

b) Experiments in vivo.

None of the experimental animals showed any evidence of nitro, or nitroso compounds.

It is our opinion that our earlier experiments demonstrate that given the in vivo conditions cited, there is no evidence of nitration, or nitrosylation, of proteins, or of other lung tissue material after inhalation of nitrogen oxide, at least not in any determinable quantity, either using our procedures, or analytical methods. This is in agreement with the findings of previously cited authors, as well as with the finding of Henschler (1966, 1965), who traced the origin of lung carcinoma in long-term experiments in animals, but failed to find the origin of carcinomas whose accidental occurrence suggested the possible development of nitrosamines after inhalation of NO_2 to which the animals were exposed. According to Neurath (1967), equimolar mixtures of NO and NO_2 are necessary for the formation of nitrosamines. In a free atmosphere, and in the mixtures used in our experiments, however, the balance is strongly shifted in favor of NO_2. Moreover, the optimum pH of the medium, 1-3, [7] for nitrosylation does not exist in vivo in lung tissue.

Our finding of nitrosyl groups in the in vitro experiments proves that these carcinogenic substances can occur only with the use of exceptionally heavy concentrations, concentrations that will cause acute poisoning in actual use.

CONCLUSION.

It has been demonstrated that the inhalation of nitrogen oxides in concentrations of from 0.01 to 0.5 mg/l in experiments on white rats will not form nitrosamines, a result that can be explained, in part, by the low concentrations of the inhaled mixtures, and in part by the relationships that exist between the individual nitrogen oxides and the pH of the medium in the respiratory pathways.

These negative chemical findings are in agreement with the findings of authors who have been following the carcinogenic effect of nitrous gases in animal experiments.

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